

General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing.

Bibliographic Source(s)

Caudle KE, Thom CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013 Dec;94(6):640-5. [40 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Gene: *DPYD*

Genetic Test Interpretation

Each named * allele is defined by the genotype at one or more specific single-nucleotide polymorphisms (Supplementary Table S1 online [see the "Availability of Companion Documents" field]). Dihydropyrimidine dehydrogenase (DPD) function associated with the most common allelic variants is summarized in Supplementary Table S2 online (see the "Availability of Companion Documents" field). Table 1 summarizes the assignment of the probable DPD phenotype on the basis of the * allele diplotypes, and these assignments are used to link genotypes with fluoropyrimidine dosing. Briefly, homozygotes of *2A, *13, and rs67376798 are considered deficient in DPD; heterozygotes for any combination of *2A, *13, and rs67376798 allele A (on the plus chromosomal strand) have intermediate or partial DPD activity; and those with none of these alleles are likely to have normal, high activity. *DPYD* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups and are summarized in Supplementary Tables S3 and S4 online (see the "Availability of Companion Documents" field). Because of conflicting data or weak evidence for alleles other than *2A, *13, and rs67376798A, the original guideline document does not currently report dosing recommendations for other variants of *DPYD*. Reports of other variants and phenotypes are discussed in the Supplementary Material online (see the "Availability of Companion Documents" field).

Table 1. Assignment of Likely DPD Phenotype Based on Genotype

Likely Phenotype	Genotypes	Examples of Diplotypes
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Likely Phenotype	Genotypes	Examples of Diplotypes
Homozygous for wild-type allele or normal, high DPD activity	An individual carrying two or more functional (*1) alleles	*1/*1
Heterozygote or intermediate activity (~3–5% of patients); may have partial DPD deficiency; at risk for toxicity with drug exposure	An individual carrying one functional allele (*1) plus one nonfunctional allele (*2A, *13, or rs67376798A)	*1/*2A; *1/*13; or *1/rs67376798
Homozygous variant or mutant; DPD deficiency (~0.2% of patients); at risk for toxicity with drug exposure	An individual carrying two nonfunctional alleles (*2A, *13, or rs67376798A)	*2A/*2A; 13/*13; or rs67376798/rs67376798A

DPD, dihydropyrimidine dehydrogenase

Drugs: Fluoropyrimidines

Dosage Recommendations

Table 2 (below) summarizes the genetics-based dosing recommendations for *DPYD* genotype and fluoropyrimidines. The strength of the dosing recommendations is based on the facts that some variants (*DPYD**2A, *13, and rs67376798) clearly affect DPD activity, DPD activity is clearly related to 5-fluorouracil clearance, and 5-fluorouracil exposure is associated with its toxic effects. Therefore, reduction of fluoropyrimidine dosage in patients with these variants may prevent severe and possibly life-threatening toxicities. However, available evidence does not clearly indicate a degree of dose reduction needed to prevent fluoropyrimidine-related toxicities. Supplementary Table S6 online (see the "Availability of Companion Documents" field) summarizes the effects of these variants on 5-fluorouracil clearance and DPD activity. Although the data suggest that patients with the *DPYD**2A variant may need a greater dose reduction than a patient with the rs67376798 variant, it is unclear to what extent the dose should be reduced. Furthermore, patients who are heterozygous for the nonfunctional *DPYD* variants mostly demonstrate partial DPD deficiency (leukocyte DPD activity at 30% to 70% that of the normal population). Thus, the authors' recommendation is to start with at least a 50% reduction of the starting dose; followed by an increase in dose in patients experiencing no or clinically tolerable toxicity, to maintain efficacy; and a decrease in dose in patients who do not tolerate the starting dose, to minimize toxicities. An alternative is pharmacokinetic-guided dose adjustment (if available). Patients who are homozygous for *DPYD**2A, *13, or rs67376798 may demonstrate complete DPD deficiency, and the use of 5-fluorouracil or capecitabine is not recommended in these patients. Because capecitabine and tegafur are converted to 5-fluorouracil and then metabolized by DPD, the clearance of and exposure to 5-fluorouracil, in addition to its toxic effects, are similar in patients with these variants.

The U.S. Food and Drug Administration (FDA) has added statements to the drug labels for 5-fluorouracil (topical only) and capecitabine that contraindicate use in patients with DPD enzyme deficiency. The FDA drug label also warns to use precaution with intravenous 5-fluorouracil in these patients. The Dutch Pharmacogenetics Working Group has evaluated therapeutic dose recommendations for 5-fluorouracil, capecitabine, and tegafur (5-fluorouracil prodrug combined with uracil; not available in United States). The Working Group recommends the use of an alternative drug for homozygous carriers of a decreased-activity allele and a reduced dose or alternative drug to capecitabine or 5-fluorouracil for heterozygous carriers of a decreased-activity allele.

At the time of the writing of the original guideline document, there were no data available on the possible role of *DPYD**2A, *13, or rs67376798 in 5-fluorouracil toxicities in pediatric patient populations; however, there is no reason to suspect that variant *DPYD* alleles would affect 5-fluorouracil metabolism differently in children as compared with adults.

Table 2. Recommended Dosing of Fluoropyrimidines by DPD Phenotype

Phenotype (Genotype)	Implications for Phenotypic Measures	Dosing Recommendations	Classification of Recommendations ^a
Homozygous for wild-type allele, or normal, high DPD activity	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity	Use label-recommended dosage and administration	Moderate
Heterozygous, or intermediate activity	Decreased DPD activity (leukocyte DPD activity at 30%–70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	Start with at least a 50% reduction in starting dose, followed by titration of dose based on toxicity ^b or pharmacokinetic test (if available)	Moderate
Homozygous, or deficient activity	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs	Select alternative drug	Strong

Fluoropyrimidines: 5-fluorouracil, capecitabine, and tegafur. DPD, dihydropyrimidine dehydrogenase.

^aRating scheme is described in the "Rating Scheme for the Strength of the Recommendations" field.

^bIncrease the dose in patients experiencing no or clinically tolerable toxicity to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cancer

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Medical Genetics

Oncology

Pharmacology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information to allow the interpretation of clinical *DPYD* genotype tests so that the results can be used to guide dosing of fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur)

Target Population

Patients requiring fluoropyrimidine chemotherapy

Interventions and Practices Considered

Dosing of fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur) based on *DPYD* genotype

Major Outcomes Considered

Rate and severity of fluoropyrimidine-related adverse events including toxicity

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A literature search of the PubMed database (1966 to March 2013) using the keywords ([DPD OR *DPYD* OR Dihydropyrimidine Dehydrogenase] AND [fluorouracil OR 5-FU OR fluoropyrimidines OR capecitabine OR tegafur] AND genotype) was performed and results were limited to those available in English. Further articles were found via the reference sections of reviews.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Clinical Pharmacogenetics Implementation Consortium's (CPIC's) dosing recommendations (see Table 2 in the original guideline document) are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account include *in vivo* clinical outcome for reference drug, *in vivo* pharmacokinetic and pharmacodynamic (PK/PD) studies for reference drug, and *in vitro* enzyme activity with probe substrate only.

The evidence summarized in Supplemental Table S5 (see the "Availability of Companion Documents" field) is graded using a modified scale (see the "Rating Scheme for the Strength of the Evidence").

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. The authors chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence based recommendations on the use of retroviral agents found at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf> (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The main benefit to the patient would be the potential to avoid toxicity by using either alternative therapy or lower fluoropyrimidine doses.

Potential Harms

- The aim is to prevent the most severe and fatal instances of toxicity, but some patients who would not have experienced this degree of toxicity and who would have benefited from fluoropyrimidine therapy may be advised against it. Moreover, heterozygous patients who receive a lower dose of a fluoropyrimidine and who would not have experienced this degree of toxicity may not experience the full benefit of fluoropyrimidine therapy; therefore, it is important to increase the dose in patients experiencing no or clinically tolerable toxicity to maintain efficacy. Patients who proceed with 5-fluorouracil therapy may still experience lower-grade toxicity that may be acceptable and even necessary in order to achieve efficacy. Some patients without a variant *DPYD* allele may still experience severe toxicity due to other genetic, environmental, or other factors.
- A possible risk is the misreporting or misinterpretation of genotype test results. This mistake could be recorded in the patient record and could also influence further treatments.

Contraindications

Contraindications

The U.S. Food and Drug Administration (FDA) has added statements to the drug labels for 5-fluorouracil (topical only) and capecitabine that contraindicate use in patients with DPD enzyme deficiency. The FDA drug label also warns to use precaution with intravenous 5-fluorouracil in these patients.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

The positive predictive value and negative predictive value of *DPYD**2A genotyping to predict development of severe toxicity (grade 3) are ~50 and ~95%, respectively; however, taking into account other variant alleles, such as rs67376798 and *DPYD**13, increases the positive predictive value to 62% (the negative predictive value remains unchanged). Furthermore, the sensitivity calculated in this study for this genotype test was only 31%; therefore, the absence of these variants does not rule out DPD defects. Although many additional variants of *DPYD* are known (see Supplementary Tables S1, S3, and S4 online [see the "Availability of Companion Documents" field]), the frequencies are often very low, and evidence for their functionality is limited.

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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Dec

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The authors declared no conflict of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [Pharmacogenomics Knowledgebase Web site](#) .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the [Pharmacogenomics Knowledgebase Web site](#) .
- An interactive dosing table is available from the [Pharmacogenomics Knowledgebase Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 9, 2014. The information was verified by the guideline developer on August 13, 2014.

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